CREOSOTE - TOXICOLOGY

1.0 EXECUTIVE SUMMARY

Creosote is a fungicide, insecticide, and sporicide used as a wood preservatives for above and below ground wood protection treatments as well as treating wood in marine environments. All 21 Creosote products currently registered are Restricted Use Pesticides; 20 are End-Use Products and 1 is a Manufacturing-Use Product for formulating industrial end-use wood preservative products. Creosote wood preservatives are used primarily to pressure treat railroad ties/crossties (represents close to 70% of all Creosote use) and utility poles/crossarms (represents 15 - 20% of all Creosote use). The industry refers to different blends of creosote [based on the wood treatment standards set by the American Wood-Preservers' Association (AWPA)], as P1/P13, P2, and P3. Typically, railroad ties/crossties are treated with a P2 blend, which is more viscous than the P1/P13 blend used for treating utility poles. The AWPA cites P3 as "Creosote-petroleum".

The toxicological database for creosote shows that for acute exposures, creosote is moderately toxic by the oral, dermal, and inhalation route, while exposure to the eye produces significant irritation. There does not appear to be any differences in acute toxic response to either the P2 or P1/P13 blend of creosote. Treatment-related effects of toxicological concern from exposure to creosote are mutagenicity and carcinogenicity, which formed the basis for the restricted use classification for creosote. Other toxicological effects of concern are cardiomyopathy resulting from inhalation exposure, and discoloration of the lungs from the presence of black pigment granules within alveolar macrophages.

Although there are no current Agency guideline neurotoxicity studies available for creosote, the existing studies on creosote indicate no evidence of neurotoxicity for either the P1/P13 or P2 blends of creosote (ATSDR, 2002). Based on the above, and realizing that creosote is currently registered only for non -food use and is a restricted use pesticide, no additional neurotoxicity testing will be required at this time.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

Creosote , as defined by the American Wood Preservers Association, is a distillate derived from coal tar, derived by the high temperature carbonization of bituminous coal. Creosote consists primarily of liquid and solid polyaromatic hydrocarbons (PAH's) and contains some tar acids and tar bases. The two major types of creosote in use are P1/P13 creosote (a straight creosote distillate used for ground contact, land, and fresh and marine water applications) and P2 creosote, used in treatment of railroad crossties.

3.0 Hazard Assessment

3.1 Acute Toxicity

Results of acute toxicity studies, primary eye and dermal irritation studies and dermal sensitization study with Creosote P1/P13 and Creosote P2 are summarized in Table 1a and 1b.

Table 1a. Acute Toxicity of Creosote P1/P13

Study Type	Animal	Results	Tox Cat	MRID No
81-1: Acute Oral	Rat	LD_{50} Male 2451 mg/kg Female 1893 mg/kg	III	43032101
81-2: Acute Dermal	Rabbit	LD_{50} Male > 2000 mg/kg Female > 2000 mg/kg	III	43032102
81-3: Acute Inhalation	Rat	LC_{50} > 5 mg/L	IV	43032103
81-4: Primary Eye Irritation	Rabbit	Irritation clearing in 8-21 days	II	43032104
81-5: Primary Dermal Irritation	Rabbit	erythema to day 14	III	43032105
81-6: Dermal Sensitization	Guinea Pig	study unacceptable	N/A	43032106

Table 1b. Acute Toxicity of Creosote P2

Study Type	Animal	Results	Tox Cat	MRID No
81-1: Acute Oral	Rat	LD_{50} Male 2524 mg/kg Female 1993 mg/kg	III	43032301
81-2: Acute Dermal	Rabbit	LD_{50} Male > 2000 mg/kg Female > 2000 mg/kg	III	43032302
81-3: Acute Inhalation	Rat	LC_{50} > 5.3 mg/L	IV	43032303
81-4: Primary Eye Irritation	Rabbit	Irritation clearing within 7 days	III	43032304
81-5: Primary Dermal Irritation	Rabbit	no irritation after 7 days	III	43032305
81-6: Dermal Sensitization	Guinea Pig	study unacceptable	N/A	43032306

3.2. Subchronic Toxicity

Reference: R.A. Hilaski; April 13, 1995; North American P1/P13 Creosote CTM: 90-Day Subchronic Dermal Toxicity Study In Rats**.** IRDC, Mattawan, MI.; Report No. 671-013. Sponsored by The Creosote Council II. MRID # 43616101 Unpublished. Study I.D. : IRDC 671-013

Executive Summary: In a 90-day dermal toxicity study (MRID # 43616101), 10 Charles River Crl:CD BR rats (10/sex/dose) were given dermal applications of P1/P13 creosote in corn oil mixture at dosage levels of 0, 4, 40 or 400 mg/kg bw/day. There were no treatment-related effects from dermal application of P1/P13 creosote on body weight, food consumption, ophthalmology, hematology, clinical chemistry, or organ weights at any dose level tested. Mortality (death of one male rat at 400 mg/kg/day) was observed on day 79 of the study. No test-article related microscpoic lesions were noted at the application site on the skin at any dose level. Based on the results of this study, the systemic LOAEL was determined to be 400 mg/kg bw/day for both male and female rats, based on mortality. The systemic NOAEL was determined to be 40 mg/kg/day.

This study is classified as **acceptable** and satisfies the guideline requirement (OPPTS 870.3250; OPP 82-3) for a subchronic dermal toxicity study in rats for P1/P13 creosote

Reference: R.A. Hilaski; April 13, 1993; North American P2 Creosote CTM: 90-Day Subchronic Dermal Toxicity Study in Rats. IRDC, Mattawan, MI.; Report No. 671-014. Sponsored by The Creosote Council II. MRID # 43616201.

Executive Summary**:** In a 90-day dermal toxicity study (MRID # 43616201), Charles River rats (10/sex/dose) were given dermal applications of P2 creosote in corn oil at dosage levels of 0, 4, 40 or 400 mg/kg bw/day. There was no mortality observed in this study at any dose level. Body weight in high dose males was decreased 7-8% during weeks 9-12 of the study, and bodyweight gain decreased 15% in high dose males for the treatment period. Food consumption in high dose males was decreased during weeks 2-4 and week 6 by 4-10% vs control. Only slight dermal irritation was observed in high dose males. No effects were observed on hematology or clinical chemistry. Treated skin in the 400 mg/kg/day dose groups (male and female) was observed with increased incidence of dermal inflamation. Based on the results of this study, the systemic LOAEL is 400 mg/kg/day, based on decreased body weight gain in male rats. The systemic NOAEL is 40 mg/kg/day. For females, the NOAEL is set at 400 mg/kg bw/day since no systemic toxic effects were noted in any of the treated groups.

Reference: R.I. Hilaski, March 28, 1995: Thirteen week subchronic inhalation toxicity study on North American P1/P13 Creosote CTM in rats.; International Research and Development Corp., Mattawan, MI 49071; Project No. 671-016; Creosote Council II; MRID # 43601001; Unpublished

Executive Summary: In a subchronic inhalation toxicity study with P1/P13 creosote (MRID # 43601001), 20 Sprague-Dawley rats/sex/group were treated for thirteen weeks, five days a week, six hours per day with P1/P13 Creosote CTM via whole body exposure at doses of 0, 5.4, 49 and 106 mg/m^3 (0.005, 0.049 and 0.106 mg/L in air, respectively) measured gravimetrically. The aerosol MMAD was between 2.2 and 3.0 microns with a geometric standard deviation between 1.91 and 1.99. Subsequent to the exposure period 10 animals/sex/group were allowed to recover for 6 weeks.

During the study one male rat of the mid dose group (49 mg/m^3) died from myocardial degeneration that resulted in heart failure. One male and one female rat in the highest dose group had similar lesions observed at terminal necropsy. Cardiac pathology (ie: hemorrhage, lymphocytic infiltration and cardiomyopathy) was noted in all animals of all groups (including controls) and this condition may have been exacerbated by treatment with creosote in the mid and high dose animals. Significant treatment-related findings in the mid and high dose animals after the exposure period included decreased body weight gains of both sexes (resolved by the end of recovery period), altered hematological parameters (decreased hemoglobin, hematocrit, numbers of erythrocytes, increased numbers of reticulocytes, polychromasia, poikilocytosis, anisocytosis - both sexes) and biochemical parameters (increased serum cholesterol levels - both sexes, phosphorous levels - males only). Macroscopic discolouration of the lungs, which persisted

throughout the recovery period, was correlated with the presence of black pigment granules within alveolar macrophages of animals of all treatment groups. An increase in liver/brain weights (statistically significant only in the females), increased lung/trachea/body weight ratios and the presence of small cystic spaces containing basophilic mucoid material in the nasal cavity epithelium was still evident after the recovery period in both sexes.

Male and female rats of the low dose group were observed to have mild poikilocytosis and anisocytosis while the females only showed the occasional cyst of the epithelium in the nasal cavity. All hematological findings in low dose animals showed recovery.

Based on the results of this study, the systemic LOAEL is 49 mg/m ^{3} for both sexes, based on cardiac pathology, decreased body weight gain, altered hematology and clinical chemistry, and gross pathological findings in the lungs. The systemic NOAEL is 5.4 mg/m^3 (0.005 mg/L) for P1/P13.

This study is classified as **acceptable** (guideline) ans satisfies the guideline requirement (OPPTS 870.3465; OPP 82-4) for a subchronic inhalation toxicity study in rats.

Reference: R. J. Hilaski; March 27, 1995; Thirteen week subchronic inhalation toxicity study on North American P2 Creosote CTM in rats.; International Research and Development Corp., Mattawan, MI 49071; Project No. 671-018; Creosote Council II; MRID # 43600901. Unpublished.

Executive Summary: In a 13-week inhalation toxicity study (MRID # 43600901), 20 Sprague-Dawley rats/sex/group were treated for 5 days/week, 6 hours/day with P2 Creosote CTM via whole body exposure at doses of 0, 4.7, 48 or 102 mg/m^3 (0, 0.005, 0.048 or 0.102 mg/L) in air measured gravimetrically. The aerosol size MMAD was between 2.4 and 2.9 microns with a geometric standard deviation between 1.85 and 1.91. Subsequent to the exposure period 10 rats/sex/group were allowed to recover from treatment for 6 weeks.

During the exposure period, two animals (low dose female; mid dose male) were sacrificed in extremis and the cause of morbidity was not related to treatment. Significant treatment-related findings in mid and high dose animals included decreased terminal body weight and body weight gain (m/f), altered hematological parameters (decreased hemoglobin content, hematocrit, erythrocyte and platelet counts; increased reticulocyte counts and mild poikilocytosis, m/f) and biochemical parameters (increased serum cholesterol levels, m/f). In both sexes macroscopic discolouration of the lungs persisted through the recovery period and correlated with the presence of black pigment granules within alveolar macrophages. Both sexes showed increased absolute and relative liver and thyroid weights and increased lung/trachea/body weight ratios. Absolute and relative thyroid weights of high dose animals actually increased after the recovery period. An increased incidence of lesions of the nasal cavity epithelium (chronic inflammation) was noted following treatment (all treatment groups, m/f) but appeared to lessen in incidence and severity

during the recovery period (mainly the high dose group, m/f). During exposure an increased incidence of thyroid follicular epithelial cell hypertrophy occurred in all male groups including control and in the high dose female group. At recovery the male incidence remained similar to that observed at exposure while the incidence in females of the high dose group had declined. The incidence of thyroid follicular cell hypertrophy was slightly increased in low and mid dose females after the recovery period. Slightly increased incidence of mild poikilocytosis was observed in all treatment groups (m/f) including the low dose group and control, which persisted through the recovery period. Low dose animals exhibited lesions of the nasal cavity epithelium which had resolved after the recovery period. Based on the results of this study, the systemic LOAEL is 48 mg/m^3 , based on decreased body weight and weight gain, altered hematology ad clinical chemistry, increased absolute and relative weight of the liver ad thyroid, and increased incidence of lesions of the nasal cavity. The systemic NOAEL is set at 4.7 mg/m^3 (0.0047 mg/L) for P2 Creosote CTM in rats.

This study is classified as **acceptable** (guideline) and satisfies the guideline requirement (OPPTS 870.3465; OPP 82-4) for a subchronic inhalation toxicity study in rats for P2 creosote.

3.3 Developmental Toxicity

Reference: Raymond York, (March 10, 1995). Developmental Toxicity Study In Rats: North American P1/P13 Creosote. IRDC, 500 North main Street, Mattawan, MI, Report number 671-020, The Creosote Council II, Mellon Hall, Duquesne University, Pittsburgh, U.S.A. MRID # 43584201. Unpublished.

In a developmental toxicity study using P1/P13 creosote (MRID # 43584201), pregnant female Sprague-Dawley rats (30/dose) were administered P1/P13 creosote at dose levels of 0, 25, 50, and 175 mg/kg/day on gestation days 6 through 15 inclusive. Decreased body weight and food consumption were observed in dams at the 175 mg/kg/day dose level. Decreased uterine weight was observed in dams at the high dose, which is reflected partly by the decreased live fetuses per litter at the high dose (although mean fetal weight was not affected). Cesarean section observations showed significantly increased resorptions and post-implantation loss as well as decreased number of live fetuses per litter at the 175 mg/kg/day dose. Based on the results of this study, the maternal NOAEL is 50 mg/kg/day, and the maternal LOAEL is 175 mg/kg/day, based on decreased body weight gain and food consumption during the study.

No treatment-related malformations (external, visceral or skeletal) were observed in any of the fetuses at 25 mg/kg bw/day. At 50 mg/kg bw/day, the overall incidence of malformations on a fetal and litter basis were statistically elevated compared to controls. However, these individual malformations were not seen at higher dose levels and/or fell within the range of historical control data. At 175 mg/kg/day there was (i) an overall significant increased incidence of developmental malformations, (ii) increased incidence of cardiovascular, vertebral and digital malformations, compared to lower dose levels, concurrent controls or historical controls (2429 and 2898 fetuses

examined viscerally and skeletally respectively) and (iii) an increased incidence of malformations at this dose level in spite of increased fetal loss (resorptions) (Beck and Lloyd, 1963) thus resulting in fewer fetuses available for teratogenic examination. Although the incidence of fetal malformations observed at 175 mg/kg/day dose level in rats was low and could be related to maternal stress (decreased body weight gain and food consumption), the teratogenic potential of P1/P13 Creosote cannot be ruled out. Based on these data, the developmental toxicity NOAEL is 50 mg/kg/day, and the developmental toxicity LOAEL is 175 mg/kg/day, based on increased post-implantation loss, increased mean resorptions, decreased live fetuses per litter, and increased developmental malformations.

This study is classified as **acceptable** and satisfies the guideline requirement (83-3) for a developmental toxicity study in rats with P1/P13 creosote.

Reference: Developmental Toxicity Study In Rats: North American P2 Creosote. Raymond G. York (March 10, 1995), IRDC, 500 North Main Street, Mattawan, MI, Report number 671-022, The Creosote Council II, Mellon Hall, Duquesne University, Pittsburgh, U.S.A. MRID # 43584202. Unpublished.

Executive Summary: In a developmental toxicity study (MRID # 43584202), pregnant female Sprague-Dawley rats (30/dose) were administered P2 creosote by gavage on gestation days 6 through 15 inclusive at dose levels of 0, 25, 75, and 225 mg/kg/day. Although decreases in body weight and food consumption were observed at all dose levels, food efficiency appeared affected only at the high dose of 225 mg/kg/day. Thus, the cesarean section effects observed at this dose (decreased implantations/dam, increased pre- and post-implantation loss, increased resorptions, decreased uterine weight) could be secondary to the decreased food efficiency observed at this dose. This distinction is a fine one, however, based on results with P1/P13 creosote in which no decrease in food efficiency was observed at a dose of 175 mg/kg, but increased resorptions, increased post-implantation loss, and decreased live fetuses per litter were observed at 175 mg/kg. The Maternal NOAEL in this study is determined to be 75 mg/kg/day, and the LOAEL 225 mg/kg/day, based on decreased food efficiency observed in maternal rats at 225 mg/kg/day.

With regards to assessing the teratogenic potential of P2 Creosote in rats, no treatment-related malformations (external, visceral or skeletal) were observed at the 25 mg/kg bw/day dose level. The single incidences of malformations [craniorachischisis, hydrocephaly and malpositioned eye (same pup)] observed at the 75 mg/kg bw/day dose level, and hydrocephaly at the 225 mg/kg bw/day dose level compared to none observed in lower dose levels, concurrent controls or historical controls (2429 and 2898 fetuses examined viscerally and skeletally respectively) were considered treatment-related. It should be noted that at 225 mg/kg bw/day one whole litter was resorbed and the number of fetuses examined at this level for visceral and skeletal malformations was approximately 50% of those examined at the mid-dose level. The developmental toxicity NOAEL is determined to be 25 mg/kg/day in this study, based on the incidences of malformations observed at 75 mg/kg/day which exceeded both concurrent and historical control incidence.

Reference: York, R. (1994): Developmental Toxicity Study in New Zealand White Rabbits: Creosote P1/P13. Laboratory Project number 672-002. Study conducted by IRDC. Unpublished.

In a developmental toxicity study in rabbits (MRID 44839802), artificially inseminated New Zealand White Rabbits (20/dose) were administered creosote P1/P13 in corn oil by gavage on gestation days 6 through 18. Doses were 0, 1, 9, and 75 mg/kg/day. At the 75 mg/kg/day dose level, increased abortions (3 rabbits vs. 0 control), reduced live fetuses (28 vs. 50 in control), and decreased implantation sites were noted in maternal rabbits. There was no significant effect of creosote P1/P13 treatment on offspring in this study. The Maternal NOAEL in this study is determined to be 9 mg/kg/day based on effects noted at 75 mg/kg/day. The Developmental NOAEL is determined to be 75 mg/kg/day, and the LOAEL > 75 mg/kg/day.

3.4 Reproductive Toxicity

Reference: Marcinowski, J. (1993). Two-Generation Reproduction/Fertility Study in Rats: Lab Project Number: 672-006. Unpublished study prepared by International Research & Development Corp.

In a two-generation reproduction toxicity study (MRID 42893201), Charles River Crl:CD rats, 26/sex/group, were dosed by gavage with P1/P13 creosote in corn oil at doses of 0, 25, 75, and 150 mg/kg/day. Pre-mating treatment phase lasted approximately 17 weeks, which may have contributed to the decreased fertility observed in this study. Systemic effects observed in this study for parental animals included a dose-related decrease in body weight during the pre-mating period at all dose levels. Salivation was observed at 75 mg/kg/day and above in the F1 generation. Effects in offspring included a dose-related decrease in growth of the F0 generation starting at 25 mg/kg/day (as shown by decreased pup weight). For the F0 pups, mean number of live pups per litter was decreased at 75 and 150 mg/kg/day, and percent live pups at 175 mg/kg/day was also decreased. In the F1 pups, the percent live pups was decreased at 75 and 150 mg/kg/day, but pup growth was affected only at 150 mg/kg/day as shown by decreased mean pup weight. Decreased fertility and pregnancy indices were observed in the F1 female parental rats at all dose levels, but this was not interpreted as a treatment-related effect, as it was more likely related to the fact that the critical weight for fertility was exceeded by the 17-week pre-mating interval. Based on the results of this study, the Parental Systemic NOAEL is < 25 mg/kg/day, and the parental systemic LOAEL is 25 mg/kg/day, based on decreased pre-mating body weight. The developmental NOAEL in this study is < 25 mg/kg/day, and the developmental LOAEL is 25 mg/kg/day, based on a dose-related decrease in pup body weight for the F0 pups from days 14-21. The reproductive NOAEL is < 25 mg/kg/day, and the reproductive LOAEL is 25 mg/kg/day, based on reduced pregnancy and fertility indices in F1 female parental rats.

3.5 Chronic Toxicity/Carcinogenicity

The chronic toxicity/carcinogenicity data base submitted to the Agency for creosote consists of a six-month initiation/promotion study of creosote conducted in mice. This study was not designed for purposes of deriving a quantitative risk estimate of carcinogenic potency. However, a recently conducted study by Culp et al. (Carcinogenesis vol. 19, no.1, pp. 117-124) did examine tumors induced by coal tar mixtures and is also summarized in this section.

Reference: Naas, D.J. (1996) A 6-month dermal oncogenicity study of creosote in mice. WIL Research Laboratories, Inc., 1407 George Road, Ashland, OH 44805-9281, Project No. WIL-100005, January 11, 1996. MRID 44844401. Unpublished.

EXECUTIVE SUMMARY: In a dermal oncogenicity study (MRID 44844401), North American P1/P13 creosote composite (100.0%, lot no. P1/13-009-A) was administered to groups of 30 male Crl:CD-1® mice by applying 50 μL aliquots of 1%, 50% or 100% corresponding to 10 μg/μL, 500 μg/μL, or undiluted creosote to the shaved backs of the mice. Acetone was utilized as a solvent throughout the study and was used as the solvent control. 9,10-Dimethyl-1,2-benzanthracene (DMBA) was utilized as a positive tumor initiator, and 12-0-tetradecanoyl-phorbol-13-acetate (TPA) was used as a positive tumor promoter in the study. Creosote was tested as a tumor initiator with TPA as promotor, as a promotor with DMBA as initiator, and as both initiator and promotor (complete carcinogen). A positive control group with DMBA and TPA, and acetone controls groups with DMBA and TPA were included. The initiation phase consisted of 5 applications/week for 2 weeks followed by a two week rest period, and then promotion (2 applications/week for 26 weeks).

Creosote treatment at 50% and 100% especially during the promotion phase caused skin irritation and clinical signs including severe erythema, slight edema, eschar, and exfoliation. Increased incidences of thickened skin (7-11/30, $p < 0.01$), scabbing (16-20/30, $p < 0.01$), acute inflammation (12-18/30, $p < 0.01$), ulceration (6-10/30, $p < 0.05$-0.01), and epithelial hyperplasia (13-23/30, $p < 0.01$) were seen at the application site during necropsy compared to the DMBA/acetone controls (0/30). Dermal treatment with Creosote did not result in a significant decrease in survival, although 6 mice died during treatment in the DMBA/100% creosote group compared to none in the acetone control groups. Group mean body weights of males treated with 100% creosote during the initiation phase were decreased by 6-8% by the end of the 2-week treatment regimen; however, they gained weight rapidly over the next week and no further decreases in weight or weight gain were seen with creosote treatment compared to the acetone controls. Food consumption in the experimental groups was generally greater than in the solvent control groups.

Increased incidences of enlarged lymph nodes were seen with 50% (6/30, $p < 0.05$), and 100% creosote (5-9/30, $p < 0.05$-0.01) during the promotion phase with DMBA as initiator and with 100% creosote as both initiator and promotor (6-9/30, $p < 0.05$-0.01) compared to 0/30 in the

solvent controls. Incidences of enlarged spleen were also increased (15-19/30, $p < 0.01$) with 50% and 100% creosote in the promotion phase compared to the controls (1/30).

The LOAEL is 50 μL of 50% or 25,000 μg/day twice/week applied to the skin for 26 weeks, based on skin toxicity, enlarged lymph nodes and enlarged spleen. The NOAEL was 50 μL of 1% or 500 μg/day applied to the skin twice/week for 26 weeks.

Topical treatment of male Crl:CD-1® mice for 2 weeks in the initiation phase of the study with all concentrations of creosote followed by treatment with TPA resulted in increased incidences of neoplasms, chiefly skin papillomas (acetone/TPA control, 0%; creosote/TPA treated, 80-90%, $p < 0.01$). Treatment twice a week for 26 weeks during the promotion phase with 50 μL of 500 μg/μL or undiluted creosote following the DMBA initiation phase resulted in tumor incidences of 100% compared to 3% in the DMBA/acetone control. Topical treatment with undiluted creosote in both the initiation and promotion phases resulted in a 100% tumor incidence compared to 0% in the acetone control group. Creosote acted as an initiator, promoter, and complete carcinogen under the conditions of this study.

This oncogenicity study in the mouse is **Acceptable/Nonguideline.** The study had numerous deficiencies that limited the information obtainable on possible systemic toxic effects, but the data demonstrated unequivocally the oncogenic nature of creosote when applied to the skin of Crl CD-1® mice. The deficiencies did not affect this outcome of the study, which was designed to assess the skin tumor initiating, promoting, and complete carcinogenicity of creasote.

Reference: Culp, S.J., Gaylor, D.W., Sheldon, W.G., Goldstein, L.S., and Beland, F.A. (1998): A comparison of the tumors induced by coal tar and benzo(a)pyrene in a 2-year bioassay. Carcinogenesis 19:1, pp. 117-124

Summary: In a study by Culp et al. (1998) female B6C3F1 mice (48 mice/group) were given coal tar samples in the diet, derived from manufactured gas plant waste sites at 0, 12, 33, 117, 333, 739, and 1300 mg/kg/day (coal tar sample 1) or 40, 120, and 346 mg/kg/day (coal tar sample 2) for 2 years. Coal tar sample 1 was a mixture of samples from seven waste sites and coal tar sample 2 was a mixture from two of the waste sites plus a third waste site with a high benzo(a)pyrene content. Significant concentration-related increases in incidence of tumors of the liver, lung, forestomach, and increased incidence of hemangiosarcoma, histiocytic sarcoma, and sarcoma were observed for both coal tar sample 1 and 2. Tumors of the small intestine were also observed in addition in those mice receiving coal tar sample1, similar to an earlier study by Culp (Polycyclic Aromatic Compounds 11: 161-168; 1996).

4.0 Dose-Response Assessment

On April 1, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicological endpoints selected for occupational and residential (dermal and inhalation) exposure risk assessments for Creosote. On September 3, 2003, the Antimicrobials Division Toxicity Endpoint Selection Committee (ADTC) met to verify the selected endpoints for long-term dermal risk assessments for creosote and inhalation risk assessment, and also discussed whether dermal and inhalation Margins of Exposure should be combined for creosote risk assessment.

As there are no existing tolerances or other clearances for residues of creosote in food, an FQPA assessment is not necessary. Potential post-application exposures to residents, including children (e.g., from use of railroad ties by homeowners), could not be assessed due to lack of exposure data. The available evidence on developmental and reproductive effects of creosote was assessed by the Health Effects Division (HED) Hazard Identification Assessment Review Committee on April 1, 1999 The committee expressed concern for potential infants and children's susceptibility of creosote, based on the severity of offspring vs. maternal effects observed with testing of creosote in the P1/P13 blend developmental toxicity study in rats at the 175 mg/kg/day dose level as well as deficiencies observed in the 2-generation reproduction toxicity study in rats.

The toxicological endpoints selected for various exposure scenarios are summarized in Table 2 below.

Table 2. Summary of Doses and Endpoints Selected for Creosote Risk Assessments.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute and Chronic Dietary			
		Acute and Chronic Dietary risk assessment not required	
Carcinogenicity (Dietary)	Creosote has been shown to exert positive mutagenic effects in vitro, and has been shown to be positive for carcinogenicity in an initiation/promotion study. Creosote has been classified as a B1 carcinogen in IRIS. Oral cancer slope factor for benzo(a)pyrene, a component of creosote, used as indicator for carcinogenic potential of creosote: 7.3 $(mg/kg/day)^{-1}$ + 50% dermal absorption.		
Short-Term (Dermal)	Oral NOAEL=50	decreased body weight gain at 175 mg/kg/day	Developmental Toxicity - Rat
	MOE = 100 (50% dermal absorption used to correct for use of oral endpoint)		
Intermediate-term (Dermal)	Dermal NOAEL = 40	Decreased body weight gain at 400 mg/kg/day	90-Day Dermal Toxicity Study in the Rat
	MOE = 100		
Long-Term (Dermal)[a]	Oral LOAEL = 25 mg/kg/day	decreased pre-mating body weight	2-generation reproduction study - Rat
	MOE = 300 (10x interspecies, 10x intraspecies, 3x for use of a LOAEL)		
Inhalation (any time period)[b]	NOAEL = 0.0047mg/m^3 MOE = 100	decreased body weight, body weight gain, altered hematology	90-day Inhalation Study in the Rat
Dermal absorption[c]	50%, estimated from ratio of oral/dermal LOAELs		

[a]after re-examination of the toxicology data, the ADTC concluded that the 2-generation reproduction toxicity study was appropriate for long-term dermal risk assessment for the following reasons: the duration of the 2-generation reproduction study is more representative of the time frame (i.e. long-term) than the 90-day dermal study, and is consistent with OPP policy regarding duration of the study vs. route of exposure; body weight gain decreases in the 2-generation reproduction toxicity study were observed in the F2 generation, supporting the time frame for the long-term endpoint (i.e. > 6 months). The 90-day dermal study effects are not as representative of the time frame for the long-term dermal risk assessment. However, the two studies can be considered co-critical studies for this endpoint. Correction of the LOAEL from the 2-generation reproduction toxicity study for dermal absorption (50%) and use of a LOAEL (3x extra UF) yields a MOE and endpoint (300 and 50 mg/kg/day) similar to the 90-day dermal toxicity study (40 mg/kg/day and MOE of 300 [extra 3x to extrapolate to long-term endpoint]).

[b]the ADTC re-examined the use of the inhalation toxicity study selected for inhalation risk assessment for creosote and concluded that a developmental toxicity study, as used for the oral and dermal risk assessments of creosote, is not appropriate for inhalation risk assessment because: (1) the inhalation toxicity study showed significant effects on body weight gain early in the study (one week) and is therefore relevant for short-term assessment (2) it is also a route-specific study; and (3) the inhalation NOAEL is more sensitive than the developmental NOAEL. Therefore, the inhalation study will remain as the study for the short-term inhalation endpoint.

[C]No dermal absorption studies for creosote are available. The HIARC estimated a dermal absorption of 50% based on the results of an oral developmental toxicity in rats and a 90-day dermal toxicity studies in the same species (rats) with similar endpoints (e.g., decrease in body weight gains). Benzo(a)pyrene has also shown a similar extent of dermal absorption (Ng et al., Toxicol. Appl. Pharamcol. 115: 216-223, 1992) and supports the HIARC's decision for creosote.

5.0 Cumulative Exposure

Section 408(b)(2)(D)(v) of FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider available information concerning the cumulative effects of a particular pesticide's residues and other substances that have a common mechanism of toxicity. As there are no tolerances for creosote, the Agency is not considering whether creosote has a common mechanism of toxicity with any other chemicals. However, based on the complex nature of the creosote mixture, components of this mixture may act in similar ways to produce the adverse effects noted for creosote.

6.0 Endocrine Disruption

EPA is required under FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all active pesticides or other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate."Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), the EPA has determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC recommendation, that program include evaluations of potential effects in wildlife may. For pesticide chemicals, EPA will use FIFRA and, to some extent that effects in wildlife may help determine whether a substance may have an effect on humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening additional hormone systems may be added to the Endocrine Disruptor Screening Program.

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, creosote may be subjected to additional screening and/or testing to

better characterize effects related to endocrine disruption.